REMARKS

Reconsideration of the present application in view of the above amendments and the following remarks is respectfully requested. Claims 1-5, 7, 11-27, 34, and 35 were pending. Applicants hereby cancel claims 1, 13, 15, 16, and 22 without acquiescence to any rejection and without prejudice to prosecuting canceled subject matter in a related divisional, continuation, or continuation-in-part application. To point out with greater particularity and more clearly define certain embodiments of Applicants' invention, new claims 36-39 have been added and claims 2-5, 7, 11, 12, 14, 17-21, 23-27, 34, and 35 have been amended. No new matter has been added to the application by these amendments. Support for the amended and new claims may be found throughout the specification, for example, at page 13, lines 19-22; page 13, line 31 through page 14, line 12; page 17, lines 22-25; page 18, lines 11-16 and 24-26; and page 36, line 31 through page 37, line 2. Upon entry of the amendments submitted herewith, claims 2-5, 7, 11, 12, 14, 17-21, 23-27, and 34-39 will be pending.

REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH (ENABLEMENT)

The Examiner rejected claims 1-5, 7, 11-27, 34, and 35 under 35 U.S.C. § 112, first paragraph, asserting that the scope of the claims is not commensurate with the disclosure of the specification. The Examiner asserts that the specification lacks enablement for claims directed to pharmaceutical compositions comprising a polypeptide that comprises an amino acid sequence at least 80% identical to SEQ ID NO:2; a fragment that comprises at least 15 amino acids of SEQ ID NO:2; or a chimeric polypeptide for inducing an immune response to any *Neisseria* species.

Applicants respectfully traverse this rejection and submit that as disclosed in the specification and recited in the instant claims, Applicants fully enabled the claimed subject matter at the time the application was filed. The claims as amended herewith are directed, in pertinent part, to pharmaceutical compositions comprising a liposome formulated with (a) at least one polypeptide that comprises an amino acid sequence at least 90% identical to the amino acid sequence set forth in SEQ ID NO : 2; (b) an immunogenic fragment comprising at least 10 contiguous amino acids of SEQ ID NO : 2; or (c) a chimeric polypeptide comprising two or more

immunogenic fragments that comprise at least contiguous 10 amino acids of SEQ ID NO:2, wherein the liposome comprises a bacterial phospholipid. Without acquiescence and to expedite prosecution of the present application, the present claims are directed to a specific embodiment, wherein the claimed compositions are capable of inducing an immune response against *Neisseria meningitidis*, and to related methods.

Applicants submit that in view of the abundant guidance and direction provided in the specification (including working examples), the advanced state of the art, and the high level of skill of a person practicing the art, the specification enables a skilled artisan to make and use the claimed compositions comprising a Neisserial surface protein A (NspA) polypeptide, or variants and fragments thereof, and related methods readily and without undue experimentation. (*See In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988)).

NspA polypeptide is a conserved cell-surface polypeptide expressed by numerous strains of *Neisseria meningitidis*, which represent divergent serogroups A, B, and C (*see, e.g.,* specification at page 4, lines 15-20, and references cited therein; U.S. Patent No. 6,287,574). The NspA gene is also present in the genome of *N. gonorrhoeae*, *N. lactamica*, and *N. polysaccharea* (*see, e.g.,* page 4, lines 9-13; U.S. Patent No. 6,287,574). Even when a bacterial polypeptide is highly conserved, such as the NspA polypeptide, a person skilled in the art would reasonably expect that the polynucleotide and the encoded polypeptide from each strain of *Neisseria meningitidis* would likely have variant nucleotide and amino acid sequences, respectively. Indeed, NspA polypeptides that share at least 90% identity with the amino acid sequence in SEQ ID NO:2 have been identified (*see, e.g.,* U.S. Patent No. 6,287,574). If a person skilled in the art desired to clone and sequence the NspA polypeptide from any *N. meningitidis* strain, the skilled person may do so using any one of several known methods practiced in the art. Furthermore, because the exemplary NspA polypeptide described in the present application induced an immune response comprising antibodies that exhibited bactericidal activity against different strains of *N. meningitidis* (*see* page 66 (Table 11); *see also* U.S. Patent No. 6,287,574), a person skilled in the art would predict that an Nspa polypeptide isolated from any one of these strains would induce a similar response, even though the amino

acid sequence would, more likely than not, not be identical to the amino acid sequence of SEQ ID NO:2.

Contrary to the assertion by the Examiner and as previously made of record, the specification provides sufficient guidance, including working examples, that teach a person skilled in the art which particular regions of the NspA polypeptide may be amenable to a substitution, deletion, or addition of an amino acid. The specification also teaches which regions comprise immunogenic epitope(s) from which immunogenic fragments may be derived and thus may be less amendable to modification. The specification describes extensive mutation, modeling, and immunological studies that teach a person skilled in the art which regions of NspA are likely to be immunogenic and which regions are expected to be less immunogenic.

The specification teaches which regions of NspA are included in transmembrane regions (*e.g.,* M1-M8) and which regions are exposed on the periplasmic side (*e.g.,* T1-T3). These regions are less likely to comprise immunogenic epitopes. By way of example, the specification describes in working examples that two peptides, between residues 41-55 and between residues 141-150 of SEQ ID NO:2, bind specifically to an antibody that does not bind to the surface of intact meningococcal cells. These two peptide regions are embedded in the meningococcal outer membrane and are thus not accessible to a bactericidal antibody (*see, e.g.,* page 48, lines 15-26).

The specification also teaches which regions are exposed on the exterior (*e.g.,* L1-L4) of the cell surface of *N. meningitidis* cells (*see* page 36, lines 15 through page 37, line 2). Site directed mutations introduced into the amino acid sequences of each of the four surface exposed loops (*i.e.,* L1-L4), showed that L3 (amino acids at positions 108-125 of SEQ ID NO:2) or L3 + L2 (amino acids 68-80 of SEQ ID NO:2) contained epitopes to which bactericidal antibodies bound (*see, e.g.,* page 48, line 5 through page 52, line 11; Table 7 (Example 5)). Thus, the specification teaches a person skilled in the art not only which regions may be less amenable to mutation, but also which amino acids within each region are less amenable to modification.

Because the specification teaches the location of the periplasmic regions, transmembrane regions, the surface exposed regions, and provides examples of immunoepitopes

within the surface exposed regions, a person skilled in the art can readily make and use a composition that comprises a liposome, as recited, and an NspA polypeptide that comprises an amino acid sequence at least 90% identical to SEQ ID NO:2 and that is capable of inducing an immune response to *N. meningitidis*. Also because the specification teaches the location and characterizes particular immunoepitopes of the NspA polypeptide, a person skilled in the art can make and use the claimed composition comprising a liposome, as recited, and a polypeptide that comprises an immunogenic fragment of at least 10 contiguous amino acids of SEQ ID NO:2, wherein the composition is capable of inducing an immune response against *Neisseria meningitidis*. Furthermore, given the abundant guidance in the specification and the knowledge in the art, a person skilled in the art can perform immunological analyses, bactericidal assays, and animal model studies for characterizing the function of an NspA polypeptide of SEQ ID NO:2, variants and immunogenic fragments thereof, readily and without undue experimentation (*see, e.g.,* page 56, line 26 through page 57, line 17 (Example 8); page 57, line 20 through page 60, line 2 (Example 9); page 60, line 6 through page 62, line 13 (Example 10); page 62, line 15, through page 66, line 15 (Example 11)). Determining whether an NspA variant polypeptide or a fragment of an NspA polypeptide has retained immunogenic activity would not amount to undue experimentation, but instead is merely a matter of permissible routine screening. (*See In re Wands*, 858 F.2d 731, 736 (Fed. Cir. 1988) ("Enablement is not precluded by the necessity for some experimentation such as routine screening.")).

Applicants respectfully submit, as previously made of record, that Rudinger hardly reflects the state of the polypeptide, antibody, or molecular biology art, or the level of skill of a person practicing these arts at the time of filing of the present application. Molecular biology methods and techniques, including mutagenesis methods, have been developed and improved, permitting a skilled artisan to introduce mutations into a polypeptide and to evaluate the effect of such mutations readily and without undue experimentation. The specification teaches positions within the NspA's polypeptide sequence that can tolerate a substitution, deletion, or insertion of an amino acid, and also teaches which positions are less amenable to modification. Also described are methods and techniques, such as immunoassays assays, to determine the ability of the protein to react with different monoclonal and polyclonal antibodies

that are specific for immunogenic and non-immunogenic epitopes (*see, e.g.,* pages 39, line 31 through page 44, line 14). While, according to Rudinger, "painstaking experimental study" may have been required in 1976 to make variants and immunogenic fragments of a polypeptide, given the extensive disclosure in the present application and given the knowledge in the art approximately 25 years later at the time of filing the instant application, such experimentation is routine. Because the present application teaches the function of the polypeptides of the claimed compositions and teaches that this function can be mapped to specific structural domains, a person skilled in the art can, readily without undue experimentation, make and use the claimed compositions.

Applicants also respectfully disagree that the cited document, Mikayama et al. (*Proc. Natl. Acad. Sci. USA* 90:10056-60 (1993)), supports the Examiner's assertion that the present specification lacks enablement for the instant claims. Mikayama et al. point out that murine and human glycosylation-inhibiting factor (GIF) polypeptide homologues exhibit the same function and have approximately 90% amino acid identity. Thus, Mikayama et al. provide an example of polypeptide variants that exhibit a high percent amino acid identity and that exhibit the same function. By contrast, a macrophage migration inhibitory factor (MIF) polypeptide shares a higher percent identity with human GIF than observed between the GIF homologues; however, human MIF exhibited an *entirely different functional activity*, which was clearly and readily demonstrated by Mikayama et al. using methods familiar to persons skilled in this art. The results in Mikayama et al. suggest that if a person skilled in the art were to make polypeptide variants using the human GIF polypeptide sequence as a starting point, the skilled person would identify variants that were highly structurally related and that exhibited the same function with far greater probability than variants that did not exhibit the same function.

As suggested in Mikayama et al., in the polypeptide art identifying a polypeptide that has lost a claimed function or property is far more unpredictable than making a polypeptide variant that has the claimed structural features and exhibits a claimed correlative function. By way of a further example, Wan et al. (*Mol. Endocrinol.* 17:2240-50 (2003), enclosed herewith) performed random mutagenesis of a 246-amino acid polypeptide and tested

whether the various mutants maintained the capability to interact with a given monoclonal antibody. Wan et al. generated and screened a library of 5200 mutagenized clones and identified only 128 clones (approximately 2.5%) that were *negative* for binding to the relevant monoclonal antibody. Thus, Wan et al. empirically showed that polypeptides can tolerate a great deal of variation, and that making a polypeptide that has lost its described function (in this example, binding to a monoclonal antibody) is less predictable than identifying polypeptide variants that *retain* their described function.

Applicants are not required, however, to demonstrate and provide disclosure for polypeptides that do not fall within the scope of the claims. Given the teachings in the instant application, the skill level of a person skilled in the art, and the knowledge in the art, the skilled person, if he or she so desires, is enabled to make variants of the *Neisseria* cell surface polypeptide with statistically far more predictability than to make a polypeptide that has lost the capability to induce an immune response against *Neisseria meningitidis*. (*See also, e.g., Molecular Biology of the Gene*, page 227 (James D. Watson et al., ed., The Benjamin/Cummings Publishing Co., (Menlo Park, CA) (4th ed. 1987) "In fact, evidence now indicates that amino acid replacements in many parts of a polypeptide chain can occur without seriously modifying catalytic activity").

Applicants submit that the scope of the present claims is commensurate with the disclosure in the specification, satisfying the requirements for enablement under 35 U.S.C. § 112, first paragraph. Applicants respectfully request that this rejection be withdrawn.

REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH (WRITTEN DESCRIPTION)

The Examiner rejected claims 1-3, 7, 11-27, 34, and 35 under 35 U.S.C. § 112, first paragraph, asserting that the claims are directed to subject matter that is not adequately described in the specification. The Examiner asserts that the specification does not describe a polypeptide comprising an amino acid sequence that is at least "70-95% identical to SEQ ID NO:2 or 15 amino acid fragments of SEQ ID NO:2 that induce an immune response to any species of *Neisseria*."

Applicants respectfully traverse this rejection and submit that, as disclosed in the specification and recited in the instant claims, the application reasonably conveys to a person skilled in the art that Applicants possessed the claimed invention at the time of filing. Applicants respectfully submit that the subject matter of the pending claims as amended herewith is adequately supported by the specification and submit that the disclosure provides sufficiently detailed, relevant, and identifying characteristics, both structural and functional, of the claimed compositions comprising a liposome formulated with an NspA polypeptide as recited. Given the recited structural features of the NspA polypeptide, variants, and fragments, and the recited functional feature that a composition comprising such an NspA polypeptide has the capability to induce an immune response against *Neisseria meningitidis*, and given the extensive description in the specification, a person skilled in the art would readily appreciate that at the time of filing Applicants possessed the species encompassed by the claims.

Description that is needed in a specification to support generic claims related to biological subject matter depends on a variety of factors, including "existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology, the predictability of the aspect at issue, and other considerations appropriate to the subject matter" (*see Capon v. Eshhar,* 418 F.3d 1349, 1359 (Fed. Cir. 2005)). Thus, the fundamental factual inquiry under the written description requirement focuses on the understanding of a person skilled in the art. See also M.P.E.P. § 2163.02.

The specification describes in particular detail, contrary to the assertion in the Action, the structure of a Neisserial surface protein A (NspA) polypeptide, or variants and fragments thereof, and correlates the structural features with the described and recited function, the capability to induce an immune response against *Neisseria meningitidis*. NspA is a conserved cell-surface polypeptide expressed by numerous strains of *N. meningitidis*, which represent divergent serogroups A, B, and C (*see, e.g.,* specification at page 4, lines 15-20, and references cited therein; U.S. Patent No. 6,287,574). The NspA gene is also present in the genome of *N. gonorrhoeae*, *N. lactamica*, and *N. polysaccharea* (*see, e.g.,* page 4, lines 9-13; U.S. Patent No. 6,287,574).

As noted above, in determining whether a claim meets the written description requirement, the PTO must recognize the state of the art and the level of skill in the art, which with respect to the pending claims, is high. *See Capon v. Eshhar*, 418 F.3d 1349, 1359 (Fed. Cir. 2005). Even when a bacterial polypeptide is highly conserved, such as the NspA polypeptide, persons skilled in the art would reasonably expect, given the rapid division time of a bacterium and the genetic adaptability of an infectious disease organism in a host, that the polynucleotide and the encoded NspA polypeptide from each strain of *Neisseria meningitidis* would likely have variant nucleotide and amino acid sequences, respectively. Indeed, NspA polypeptides that share at least 90% identity with the amino acid sequence in SEQ ID NO:2 have been identified (*see, e.g.,* U.S. Patent No. 6,287,574). The present application need not describe these NspA variants; the specification need only describe what is new or not conventional (*see, e.g., Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986)). Moreover, the exemplary NspA polypeptide (SEQ ID NO:2) is capable of inducing an immune response that included antibodies that were bactericidal for heterologous strains of *N. meningitidis*, showing that the immunogenic epitopes of the single species represented by SEQ ID NO:2 is capable of inducing antibodies that binds to other species (*i.e.,* NspA polypeptide variants) within the claimed genus (*see* page 66, Table 11). Thus, a person skilled in the art would readily appreciate and understand that Applicants possessed NspA variants.

Applicants therefore respectfully disagree with the assertion by the Examiner that adequate written description of claims related to a genus of polypeptides requires that the specific amino acid sequence of each protein itself must be provided (*see, e.g.,* Action, page 8). Such a description is not required under 35 U.S.C. § 112, first paragraph, as the written description requires neither examples nor an actual reduction to practice. *See Falko-Gunter Falkner v. Inglis,* 448 F.3d 1357, 1366 (Fed.Cir.2006). ("A claim will not be invalidated on section 112 grounds simply because the embodiments of the specification do not contain examples covering the full scope of the claim language.") ("An actual reduction to practice is not required for written description.").

Contrary to the assertion by the Examiner and as previously made of record, the specification provides guidance, including working examples, that teach a person skilled in the

art which particular regions of the NspA polypeptide may be amenable to a substitution, deletion, or addition of an amino acid. The specification describes extensive mutation, modeling, and immunological studies that teach a person skilled in the art which regions of NspA are likely to be immunogenic and which regions are expected to be less immunogenic. The specification also teaches which regions comprise immunogenic epitope(s) from which immunogenic fragments may be derived and thus may be less amendable to modification.

The specification describes amino acid positions of NspA that are included in transmembrane regions (*e.g.,* M1-M8) and describes which regions are exposed on the periplasmic side (*e.g.,* T1-T3). These regions are less likely to comprise immunogenic epitopes. By way of example, the specification further describes in working examples that two peptides, between residues 41-55 and between residues 141-150 of SEQ ID NO:2, bind specifically to an antibody that does not bind to the surface of intact meningococcal cells. These two peptide regions are embedded in the meningococcal outer membrane and are thus not accessible to a bactericidal antibody (*see, e.g.,* page 48, lines 15-26).

The specification also teaches which regions are exposed on the exterior (*e.g.,* L1-L4) of the cell surface of *N. meningitidis* cells (*see* page 36, lines 15 through page 37, line 2). Site directed mutations introduced into the amino acid sequences of each of the four surface exposed loops (*i.e.,* L1-L4), showed that L3 (amino acids at positions 108-125 of SEQ ID NO:2) or L3 + L2 (amino acids 68-80 of SEQ ID NO:2) contained epitopes to which antibodies that exhibit bactericidal activity bound (*see, e.g.,* page 48, line 5 through page 52, line 11; Table 7 (Example 5)). Thus, the specification teaches a person skilled in the art not only which regions may be less amenable to mutation but also which amino acids within each region are less amenable to modification.

A disclosure naming a single species can support claims to a genus if, as here, the disclosure conveys to a person skilled in the arts the characteristics common to all species. *See In re Curtis*, 354 F.3d 1347, 1355 (Fed. Cir. 2004). A disclosure of a single species may not be sufficient under the written description requirement when the evidence indicates that a person skilled in the art could not predict the operability of any species other than the one disclosed. *Id.* at 1358. Under this predictability standard, the court in *In re Curtis* rejected appellant's genus

claims, declaring that the claims were unsupported by the disclosure of a single species. The description relied upon in *In re Curtis*, however, is distinguishable from the present application, in that the description in the Curtis application recited only the common functional properties of the claimed genus and did not provide a structural description of the genus. *See Id.* at 1355. By direct contrast, Applicants have provided much more than a functional description.

As discussed herein, Applicants have described the recited structural features of the claimed polypeptides according to common terminology used in the art (at least 90% identity to the amino acid sequence of SEQ ID NO:2 and immunogenic fragments of at least 10 contiguous amino acids of SEQ ID NO:2), and have correlated those structural features with the recited functional characteristics (*i.e.,* capability to induce an immune response to *N. meningitidis*). Thus, in view of the state of the art, given the present description and the high skill level, a person skilled in the art could envision and readily predict that many species would be operable other than those disclosed. The likelihood of producing a functional variant is increased when a polyclonal antibody response is induced. For example, Lipman et al. teach that "because [polyclonal antibodies] are heterogeneous and recognize a host of antigenic epitopes, the effect of change on a single or small number of epitopes is less likely to be significant." Lipman et al., *ILAR Journal*, 46: 258-268, 261, Col. 1 (2005) (enclosed herewith for the Examiner's convenience). By way of specific example, Wan et al. (*Mol. Endocrinol.* 17:2240-50 (2003), submitted herewith) prepared a library of 5200 polypeptide variants and detected only 125 (less than 2.5%) that no longer specifically bound to an antibody of interest. Therefore, given the existing knowledge in the art and the extent and content of the prior art, and given the extensive description in the present specification, the present application sufficiently describes the claimed subject matter and the written description requirement has been satisfied.

The basic policy of the Patent Act is to encourage disclosure. *In re Angstadt,* 537 F.2d 498, 503 (CCPA 1976) ("To require disclosures in patent applications to transcend the levels of knowledge of those skilled in the art would stifle the disclosure of inventions in fields man understands imperfectly."). The court in *In re Angstadt* states that "depriving inventors of claims which adequately protect them and limiting them to claims which *practically invite appropriation of the invention* while avoiding infringement inevitably has the effect of

suppressing disclosure." *Id.* at 504 (emphasis added). In particular, if the presently claimed subject matter is limited only to compositions comprising a polypeptide comprising a single, disclosed sequence (*e.g.,* SEQ ID NO:2), a person skilled in the art can readily, and with trivial effort, make polypeptides that are outside the scope of the claim using routine, commonly practiced techniques.

An assertion that the written description requirement is not met unless specific amino acid sequences of each species encompassed by a genus are disclosed grossly underestimates the level of skill and understanding of a person skilled in the microbiology, polypeptide, and immunological arts. Limiting the claims to the amino acid sequence set forth in SEQ ID NO:2 will inevitably invite appropriation of Applicants' inventive efforts related to compositions comprising NspA polypeptides. Moreover, when a person skilled in the art can readily make polypeptides outside the scope of the amino acid sequence of SEQ ID NO:2 that have the recited functions, the person skilled in the art would readily recognize that the application has reasonably conveyed that Applicants possessed the claimed compositions comprising a genus of NspA polypeptide variants having 90% or greater sequence identity to SEQ ID NO:2, which are capable of inducing an immune response to *N. meningitidis*.

Accordingly, Applicants submit that the specification describes the claimed compositions comprising NspA polypeptides, variants and immunogenic fragments thereof, with sufficient, relevant, identifying characteristics to convey to a person skilled in the art that Applicants possessed the claimed embodiments at the time the Application was filed. Thus, all pending claims satisfy the written description requirement under 35 U.S.C. § 112, first paragraph, and Applicants respectfully request withdrawal of the rejection.

REJECTIONS UNDER 35 U.S.C. § 103

The Examiner rejected claims 1-5, 7, 11-27, 32, 34, and 35 under 35 U.S.C. § 103, alleging that the claimed subject matter is obvious over Brodeur et al. (WO 96/29412) (Brodeur) in view of any one of Ward et al. (*Microbiol. Pathogenesis* 21:499-512 (1996)) (Ward); Idänpään-Heikkilä et al. (*Vaccine* 13:1501-508 (1995)) (Idänpään-Heikkilä); or Wright et al. (*Infect. Immun.* 70:4028-34 (2002)) (Wright). The Examiner also rejected claims 1-5, 7,

13-27, 32, 34, and 35 under 35 U.S.C. § 103, alleging that the claimed subject matter is obvious over any one of Cadieux et al. (*Infect. Immun.* 67:4955-59 (1999)) (Cadieux); Plante et al. (*Infect. Immun.* 67:2855-61 (1999)) (Plante); or Martin et al. (*J. Exp. Med.* 185:1173-83 (1997)) (Martin) in view of any one of Ward, Idänpään-Heikkilä, or Wright. The Examiner asserts that each of Brodeur, Cadieux, Plante, and Martin teach a *Neisseria* polypeptide comprising SEQ ID NO:2 and fragments thereof, and that Ward, Idänpään-Heikkilä, and Wright teach incorporation of *N. meningitidis* proteins with liposomes and that a person having ordinary skill in the art would have found it obvious to combine the teachings of any one of Brodeur, Cadieux, Plante, and Martin with Ward, Idänpään-Heikkilä, or Wright to obtain the claimed subject matter.

Applicants traverse this rejection and submit that the Examiner has not established a *prima facie* case of obviousness. *See In re Mayne*, 104 F.3d 1339 (Fed. Cir. 1997) (The USPTO has the burden of showing a *prima facie* case of obviousness). The Examiner must, at a minimum, demonstrate that either a single reference or a combination of the cited references teaches or suggests all the features of the claim. If the combination of references teaches each claim feature, the Examiner must provide an explicit, apparent reason why a person having ordinary skill in the art would combine these features in the fashion claimed by the Applicants with a reasonable expectation of successfully obtaining the claimed subject matter. *See KSR v. Teleflex, Inc.,* 237 S. Ct. 1727, 1741 (2007) ("[A] patent composed of several elements is not proved obvious merely by demonstrating that each element was, independently, known in the prior art.").

Applicants submit that each of the cited documents, alone or in any combination, fails to teach or suggest each feature of the currently pending claims. None of the cited documents, Brodeur, Cadieux, Plante, or Martin, teaches or suggests a pharmaceutical composition that combines a liposome comprising a bacterial phospholipid with a NspA polypeptide (*e.g.,* SEQ ID NO:2), variants or fragments thereof. Similarly, each of Ward, Idänpään-Heikkilä, and Wright fails to teach or suggest that a pharmaceutical composition comprising a liposome that comprises a bacterial phospholipid and which is combined with an NspA outer membrane protein.

Ward instead describes liposomes composed of phosphatidylcholine and cholesterol that are combined with the class 1 porin (the *porA* gene product) only if the porin is expressed as a fusion polypeptide (*see* Ward, page 503). Idänpään-Heikkilä describes producing the class 1 porin in *Bacillus subtilis* and reconstituting the polypeptide with phosphatidylcholine (*see* Idänpään-Heikkilä, page 1501 (abstract); page 1502, second column). Wright also describes liposomes composed of phosphatidylcholine and cholesterol that are combined with the PorB outer membrane protein (*see* Wright, page 4029, second column). None of Ward, Idänpään-Heikkilä, and Wright describes combining an NspA polypeptide with a liposome comprising a bacterial phospholipid. These cited documents teach or suggest the use of phosphatidylcholine-containing liposomes only with a particular Neisserial polypeptide other than NspA.

Furthermore, viewing the prior art as a whole, the prior art teaches that preparation of an immunogenic composition is dependent upon the particular combination of antigen, liposome, and adjuvant. As previously made of record, the teachings of the references fail to indicate that by combining the references, a person having ordinary skill in the art will achieve the claimed invention with a reasonable expectation of success. Each of Ward, Idänpään-Heikkilä, and Wright instead suggest that the success of combining the antigen respectively described therein with a liposome to prepare an immunogenic composition is variable and unpredictable. Ward determined that the *porA* gene fragment (*i.e.,* class 1 porin) was successfully expressed as a recombinant polypeptide only when fused to a bacteriophage coat protein. In addition, the composition comprising a phosphatidylcholine-containing liposome and the class 1 outer membrane porin more effectively induced bactericidal antibodies when the liposome/porin composition was administered to rabbits in the absence of an additional adjuvant (*see* Ward, Figure 4; discussion, last full paragraph; *see also* Idänpään-Heikkilä). By contrast, addition of an adjuvant to a phosphatidylcholine-containing liposome composition comprising the PorB outer membrane protein enhanced the immunogenicity of PorB (*see* Wright).

Wright teaches that the addition of adjuvant to a PorB-liposome composition is similar to that observed when a *Neisseria* Opc protein was combined with a liposome and contrasts this observation with data obtained using PorA. Wright points out that even though the

PorA and PorB share significant amino acid sequence homology and both are believed to adopt a β-barrel confirmation in the outer membrane, the two porins have significant differences that contribute to the differences in how each of the two outer membranes may be combined with a phosphatidylcholine-containing liposome composition or a phosphatidylcholine-containing liposome plus adjuvant composition to obtain an immunogenic composition that might be useful as a vaccine against meningococcus (*see, e.g.,* Wright, at page 4033, column 1, full paragraph). Totally absent from the teachings or discussion in any of Wright, Ward, or Idänpään-Heikkilä, is any speculation, much less suggestion or teaching, of how to obtain Applicants' claimed compositions comprising a liposome comprising a bacterial phospholipid and an NspA polypeptide (or variant or fragment thereof), as recited.

Thus, even if a person having ordinary skill in the art could combine the teachings of the cited art to achieve all the features of Applicants' invention, the cited documents fail to indicate which of the combinations of liposomes and adjuvants may be combined with the polypeptide comprising the amino acid sequence set forth in SEQ ID NO:2, or fragments or variants thereof, such that a person having ordinary skill in the art would obtain the compositions described and claimed in the present application with any reasonable expectation of success.

Applicants respectfully submit that the PTO has not established a *prima facie* case of obviousness and that the claimed subject matter is nonobvious as required under 35 U.S.C. § 103. Applicants therefore respectfully request that the rejection of the claims be withdrawn.

Applicants respectfully submit that claims 2-5, 7, 11, 12, 14, 17-21, 23-27, and 34-39 in the application are allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

The Director is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

Respectfully submitted,

SEED Intellectual Property Law Group PLLC

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Enclosure: Supplemental Information Disclosure Statement

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